

REMARKS

Claims 2-11 are pending and are rejected.

Claim 11 is amended, supported in the originally filed application at least at p. 3 first full paragraph and the last sentence of each of Example 1, 2, and 3, thus introducing no new matter.

Claims 12 and 13 are added; claim 12 is claim 11 with "prevention" deleted, and claim 13 is claim 11 with the amount limitations deleted. The new claims thus introduce no new matter.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 2-11 are rejected under 35 U.S.C. §112 ¶1 as not enabled "for the manufacture of a preparation for prevention of osteoporosis".

Applicants respectfully disagree. The nature of invention, breadth of claims, state of the art, predictability of the art, and amount of direction and guidance provided, are such that the invention is communicated to the public in a meaningful way, and informs the public how to make and how to use the invention, which are the standards for enablement.

Applicants' specification does provide the public enablement for prevention of osteoporosis, because it enables treatment of osteoporosis. By analogy, the public knows, for example, that consuming an apple when hungry, would also prevent hunger. The public knows, for another example, that consuming an aspirin for the treatment of a headache, would also prevent a headache. The public knows, for yet another example, that consuming an aspirin upon symptoms of a heart attack, prevents further damage; in fact, aspirin is now advertised in the popular media with indications to consume on a daily basis for the prevention of a heart attack.

Applicants apply the same principle, that is, that a product known to treat a condition (hunger, headache, heart attack, osteoporosis) also enables one to use that product to prevent that condition. Moreover, hyaluronate is a component of animal-originated food products, thus it, like an apple, is not toxic, even administered over a long period.

Applicants' Example 4 disclosing that consuming hyaluronic acid treats osteoporosis, evidenced by bone density returning to normal levels, and also evidenced by excretion of a metabolite of bone-matrix breakdown returning to normal levels. Thus, the public would conclude, because treatment was efficacious, prevention would also be efficacious. The public is thus informed how to use the invention, as required for enablement.

Further to the Examiner's p. 4 analysis on the state of and predictability or unpredictability of the art, Applicants assert that the Stančíková et al. reference (International Journal of Tissue Reactions (2004), 26 (1/2), 9-16), supports Applicants' position. Stančíková demonstrates that the formation of decomposition products of the bone collagen is practically normalized (level of natural metabolic turnover of bone collagen) by oral administration of hyaluronate. The decomposition of the bone mass does not occur due to the influence of the stated risk factors to which the Examiner cites; these factors just modify

the disease frequency and course. Thus, Applicants' respectfully assert that the skilled artisan would not have reason to doubt whether osteoporosis could be prevented, based on Stančíková.

Applicants respectfully assert enablement need not encompass such detailed information as to meet requirements for submission to the U.S. Food and Drug Administration (FDA). *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995) and MPEP §2107.

Claims 2-11 are rejected under 35 U.S.C. §112 ¶2 as indefinite. Applicants have amended independent claim 11 to recite that the claimed method of manufacture includes instructions for using the composition. The amendment is supported at least by the last sentence of each of Examples 1, 2, and 3, each describing different manufacturing methods and each concluding with directions for use.

Applicants respectfully assert that these rejections are thus overcome and respectfully request their withdrawal.

CLAIM REJECTIONS UNDER 35 U.S.C. §102

Claims 2, 4, 7, 9, and 11 are rejected under 35 U.S.C. §102(b) as anticipated by Petito.

As amended, claims 2, 4, 7, 9, and 11 recite that instructions for use are provided in the method, and also that the method of manufacture includes an amount ensuring that the daily dose of every single form of administration contains from 5 to 300 mg of the physiologically acceptable salt of hyaluronic acid.

Petito does not disclose this. Petito's manufacture requires three other active components, in addition to sodium hyaluronate. Thus, in Petito's manufacture, four active components are necessary. This is because, in Petito, all four components constitute the "chondroprotective agent" (by definition, an agent that both treats and prevents disease), and because all four components act synergistically.

Thus, the present invention is directed to a nutritional composition comprising a therapeutically effective amount of a chondroprotective agent, preferably in combination with at least one other physiologically beneficial agent. The present nutritional composition comprises about 1-30 mg/kg of a glucosamine salt, about 1-15 mg/kg of chondroitin sulfate, about 1-30 mg/kg of collagen and about 1-15 mg/mg of sodium hyaluronate, which synergistically act as the chondroprotective agent. (Petito ¶ 20)

In contrast, Applicants' composition contains only the physiologically acceptable salt of hyaluronic acid as the active. See, e.g., each of Examples 1, 2, 3, and 4, in which the only active is a sodium or calcium hyaluronate salt.

Petito discloses "nutritional compositions", stating that they

...effectively provide foundational support for the creation of new body tissue and cartilage growth, facilitate chondrocyte synthesis, protect and maintain healthy muscle and tissue, increase hyaluronic acid concentrations, and reduce inflammation...

Petito's nutritional composition is thus a fortified food or a dietary supplement that provides health benefits in addition to its basic nutritional value. In contrast, Applicants' claim a method of manufacturing a dietary preparation, which provides health benefits apart from any basic nutritional value.

For at least these reasons, Applicants assert that Petito does not anticipate claims 2, 4, 7, 9, and 11, and respectfully requests the rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 2 and 4-11 are rejected under 35 U.S.C. §103(a) as obvious over Petito in view of Leneau, or Leneau in view of Petito.

Applicants assert their above distinctions over Petito.

As the Examiner stated, Leneau does not anticipate Applicants' claim 11 range, but asserts that "It would have been obvious ...to incorporate Petito's nutritional compositions into the food and beverage formulation taught by Leneau."

Petito in view of Leneau, or Leneau in view of Petito, would not render Applicants' method of manufacture obvious, at least because Petito requires four components, acting synergistically, to result in Petito's "chondroprotective agent". A person of ordinary skill in the art would not be taught, suggested, or motivated, nor would the person predict, that a physiologically acceptable salt of hyaluronic acid without the other three components, would provide the chondroprotective agent.

Petito teaches dose ranges from 1 mg/kg to 15 mg/kg. Leneau teaches dose ranges from 0.1 µg/kg to 400 µg/kg. A person of ordinary skill in the art would not combine Petito and Leneau or Leneau and Petito because of the different dose range each teaches. The dose range of Petito is much higher, in the range of mg/kg, and does not overlap the dose range of Leneau which is much lower, in the range of µg/kg. In contrast, Applicants' claims require formulating an amount of hyaluronic acid in a composition, not a concentration. For an average 70 kg man, Applicants' concentration ranges from 0.071 mg/kg to 4.23 mg/kg. These ranges are higher than Leneau's range, lower than Petito's lower range, and only about one-third of Petito's upper range. Thus, a person of ordinary skill in the art would not find it obvious to use a range outside of Leneau's entire range and lower and only about one-third of the entire Petito range.

The Examiner states "It is noted that "for prevention and treatment of osteoporosis" does not further limit the claims. However, because the amended claims require that instructions for using the composition are provided, Applicants assert that "for prevention and treatment of osteoporosis" does limit the claims, e.g., these instructions would provide the level of the consumption required to prevent and treat osteoporosis.

Each of Petito and Leneau teach prevention or treatment of osteoarthritis. Applicants' method, in contrast, is provided with instructions for using the composition for prevention or treatment of osteoporosis. Osteoarthritis and osteoporosis are different conditions, and a teaching of preventing or treating osteoarthritis, does not render obvious preventing or treating osteoporosis, at least for the reasons subsequently explained.

In each of Petito and Leneau, the target of the orally administered hyaluronate is cartilage, which is formed of chondrocytes. In Applicants method, the target of the orally administered hyaluronate is

bone, which is formed of osteoblasts (the cells forming the bone mass) and osteoclasts (cells resorbing the bone mass).

Petito's "chondroprotective agent" is, to a person of ordinary skill in the art, one that retards degradation of articular cartilage and promotes chondrocyte metabolism in the treatment of osteoarthritis; e.g., U.S. Patent No. 5,621,009 specifies that a "chondroprotective agent" is one that protects cartilage. Thus, Petito discloses and teaches formulations for cartilage diseases, not bone diseases.

Leneau, similarly, teaches formulations for osteoarthritis (cartilage diseases, not bone diseases, e.g., claim 1 "A method for relieving joint pain or other discomforts associated with osteoarthritis in a warm-blooded vertebrate..."; col. 1 lines 9-12; col. 2 lines 2-5 and 37-43).

A person of ordinary skill in the art will thus not look to Petito or Leneau, because this person would appreciate that osteoarthritis and osteoporosis are different types of diseases that affect different parts of the body, that there are large differences between osteoarthritis and osteoporosis, and between the cartilage and the bone as well. For example,

- Osteoporosis is a disease of bones, while osteoarthritis or osteoarthritis is a disease of cartilage. Osteoarthritis and osteoarthritis are not synonyms: osteoarthritis defines a degenerative disease; osteoarthritis defines an inflammatory disease.
- Osteoarthritis or osteoarthritis is associated with changes in hyaluronate production in the articular fossa, and with deterioration of the cartilage surface. Osteoporosis is associated with a reduction of the calcium content and bone mass content in the bone.
- Cartilage is an elastic tissue that ensures smooth movement of joints. Cartilage is formed mainly by the extracellular matrix containing type II collagen and specific proteoglycans. Cartilage is relatively high hydrated. Cartilage contains cells (chondrocytes) that synthesize type II collagen only, not any other type of collagen. If type I collagen appears within the cartilage, the cartilage loses its properties and calcification, i.e. its modification to bone, may begin. In contrast, bone is a very hard tissue containing type I collagen that is formed by osteoblasts and is calcified.
- The metabolic modification in the cartilage occurs in absence of any other cells, meaning that the cartilage mass is continuously decomposed by enzymes that are produced by chondrocytes, and is replaced by a new extracellular matrix which is again produced by chondrocytes. In bone, the bone mass is produced by osteoblasts and is decomposed (resorbed) by osteoclasts. Thus, two types of cells, each having a contrary function to the other, participate in bone metabolism. The important feature for maintaining the mineral density of the bone and for the development of osteoporosis is the equilibrium between osteoblast and osteoclast activity. If the osteoclast activity predominates, then the mineral density of the bone decreases and osteoporosis increases.
- Bone is nourished by the blood, which means that capillaries lead to the bone; this is the way that orally administered hyaluronate gets into the bone. In contrast, cartilage does not have any

capillary supply and is nourished solely by diffusion. Applicants assert that, to their knowledge, no one has ever described how and if orally administered hyaluronate gets into cartilage, and to their knowledge that there are no literature references that orally administered hyaluronate influences cartilage quality and that it does heal osteoarthritis or osteoarthritis.

These are factual distinctions between cartilage and bone, and between the conditions of osteoarthritis or osteoarthritis and osteoporosis, and a person of ordinary skill in the art would not be taught, motivated, nor would this person predict that the claimed method, which includes instructions for using the composition in a dietetic preparation for prevention and treatment of osteoporosis, based on Petito, Petito in view of Leneau, or Leneau in view of Petito.

Applicants respectfully assert that none of Petito, Petito in view of Leneau, or Leneau in view of Petito, disclose, teach, motivate, or suggest manufacture of an orally administered formulation of hyaluronic acid for preventing or treating osteoporosis.

Claim 3 is rejected under 35 U.S.C. §103(a) as obvious over Petito in view of Leneau, or vice versa, and further in view of Takahashi. Applicants assert their above distinctions over Petito in view of Leneau, and Leneau in view of Petito. A person of ordinary skill in the art would not consider that Takahashi's teaching, of the calcium hyaluronate salt instilled in the bladder, would render obvious the claimed "dietetic preparation". As only one distinction, consumption of a dietetic preparation is self-controlled, installation in the bladder is not self-controlled. In addition, Takahashi's teaching does not overcome Applicants' distinctions over the primary references. Applicants thus assert that Takahashi does not render claim 3 obvious.

For at least these reasons, Applicants assert that Petito in view of Leneau, or Leneau in view of Petito, does not render claims 2 and 4-11 obvious, and further in view of Takahashi does not render claim 3 obvious. and respectfully requests the rejections be withdrawn.

CONCLUSION

Applicants believe the application is in complete condition for allowance and authorize credit card payment of the fee to Request Continued Examination (see Electronic Fee Calculation sheet). If additional fees are deemed necessary, the Office is authorized to charge them to Deposit Account No. 20-0809.

The Examiner is invited to telephone Applicants' undersigned representative with questions.

Respectfully submitted,
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